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Nutrition Discussion Forum

Vitamin E supplementation may transiently increase tuberculosis risk in males who smoke heavily and have high dietary vitamin C intake – reply by Hemilä & Kaprio

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Randomisation of participants in two study groups leads to groups that have baseline differences accountable by the play of chance. In small trials, the random variation between two study groups can be large, but in large studies the variation is typically small.

When we compare the Alpha-Tocopherol Beta-Carotene Cancer Prevention (ATBC) Study participants with high dietary vitamin C intake⁽¹⁾ administered vitamin E (*n* 6734) with those not administered vitamin E (*n* 6768), the average BMI and age are equal within 1 % accuracy: 26.43 v. 26.50 kg/m² and 57.35 v. 57.30 years, respectively. Previously, we reported that being widowed, living in a village or the countryside, and smoking \geq twenty-six cigarettes per d at the baseline were associated with a significantly higher risk of tuberculosis⁽²⁾. Among the participants with a high vitamin C intake, the distribution of these characteristics is also balanced with great accuracy in the vitamin E and no-vitamin E groups: 187 v. 187, 2296 v. 2397, and 1181 v. 1092 participants, respectively.

To propose that the 72 % higher incidence of tuberculosis in the vitamin E-supplemented participants might be explained by the maldistribution of a strong risk factor requires that the risk factor should be over 72 % more prevalent in the vitamin E-supplemented group. Given the closely equal distribution of the five risk factors described above, there is no justification to assume that any other risk factor would be unbalanced to such a degree that it could explain the 72 % difference between the two groups.

Finally, the initiation of vitamin E supplementation provides a reasonable explanation for the rapid increase in tuberculosis incidence after randomisation in the heavy smokers with high vitamin C intake (see Fig. 1 of Hemilä & Kaprio⁽¹⁾). Such a sudden effect of brief duration cannot be explained by a risk factor that is permanent or long lasting before randomisation.

In our study⁽¹⁾, we referred to the original ATBC Study reports for a detailed description of the design and methods. Potential participants were excluded from the study, for example, for proven malignancy other than non-melanoma skin cancer or carcinoma *in situ*, chronic renal insufficiency, cirrhosis of the liver, chronic alcoholism, or medical problems that might limit participation for 6 years⁽³⁾. However, the exclusion or inclusion of such participants is not related to the validity of the vitamin E supplementation analysis, because, if included, they would have been equally divided between the intervention groups. In our study⁽¹⁾, we excluded active tuberculosis cases that occurred before

randomisation. We described that most probably the majority of our participants had latent tuberculosis infection from their youth. However, this does not mean misclassification. Most individuals with latent tuberculosis infection live their lives without getting active tuberculosis; for example, globally about 2000 million individuals have latent tuberculosis infection, but only 8 million new cases of active tuberculosis occur annually⁽⁴⁾. If vitamin E supplementation increases the risk of activation of latent tuberculosis in certain population groups, as our study suggests, vitamin E supplementation should be discouraged in particular in developing countries in which latent tuberculosis is prevalent.

A particular strength of large randomised trials is that potential risk factors need not be assessed at the baseline because they are distributed close to equally between the study groups. No great increase in statistical sensitivity is likely to be conferred by stratification and/or adjustment for prognostic features in large trials⁽⁵⁾. It has even been argued that 'collecting less information may mean bigger numbers and hence better science: many trials still collect ten or a hundred times too much information per patient (which) may, paradoxically, substantially reduce the reliability with which therapeutic questions are answered, if their indirect effect is to make randomised trials smaller'⁽⁶⁾.

In our study, the interaction between vitamin E supplementation and dietary vitamin C intake was statistically significant ($P=0.042$), which justified the examination of the vitamin C subgroups separately⁽¹⁾. Nevertheless, even if all the ATBC Study participants (*n* 29 023) are examined together, the lower limit of the CI for the vitamin E effect on tuberculosis risk (-13 to $+59$ %), and the lack of interaction with age⁽¹⁾, refutes the proposal that vitamin E supplementation would lead to generalised benefits on the immune system in elderly individuals⁽⁷⁾.

We declare no conflict of interest.

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